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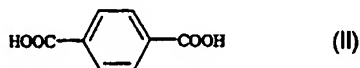
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- (71) Applicant (for all designated States except US): H. LUNDBECK A/S [DK/DK]; John Meidahl Petersen, Ottiliavej 9, DK-2500 Valby (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): PETERSEN, Hans [DK/DK]; Guldagervej 11, DK-2720 Vanløse (DK). DAHLBERG NIELSEN, Poul [DK/DK]; Prejlerupvej 26, DK-4560 Vig (DK).
- (74) Common Representative: H. LUNDBECK A/S; John Meidahl Petersen, Ottiliavej 9, DK-2500 Valby (DK).
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(54) Title: METHOD FOR THE PREPARATION OF 5-CARBOXYPHTHALIDE



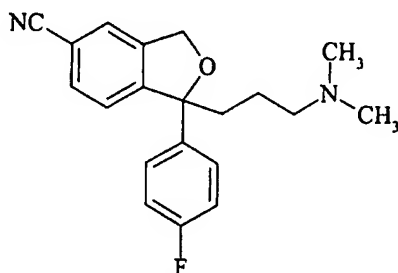
(57) Abstract: 5-carboxyphthalide is obtained with very high purity and in high yields by a convenient process comprising reaction of terephthalic acid represented by formula (II), with paraformaldehyde $\text{HO}(\text{CH}_2)_n\text{H}$ in oleum.

METHOD FOR THE PREPARATION OF 5-CARBOXYPHTHALIDE

The present invention relates to a novel process for the preparation of 5-carboxyphthalide, a starting material for the manufacture of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention

Citalopram is a selective serotonin reuptake inhibitor which has successfully been marketed as an antidepressant drug for some years. It has the following structure:



Formula I

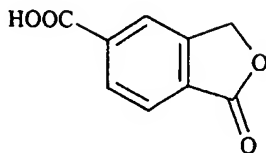
and it may be prepared by the process described in US Patent No 4,650,884 according to which 5-cyanophthalide is subjected to two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively, and the resulting dicarbinol compound is subjected to a ring closure reaction by dehydration. The 5-cyanophthalide may in its turn be obtained by reaction of 5-carboxyphthalide with a dehydrating agent and a sulfonamide of the formula H_2N-SO_2-R wherein R is NH_2 , alkyloxy, optionally substituted phenyloxy, or substituted phenyl in order to obtain 5-cyanophthalide, cf. our co-pending Danish patent application No. PA199801718.

5-Carboxyphthalide has been described as a useful intermediate in the polymer and paint industry. However, no reliable commercial source is available at present. A known process comprises catalytic hydrogenation of trimellithic acid (DE-A1 2630927). This process provides a mixture of the 5- and 6-carboxyphthalides and, accordingly, it requires elaborate and costly purification. According to J. Org. Chem. 1970, 35, p. 1695-1696, 5-carboxyphthalide is synthesised by reaction of terephthalic acid with trioxane in liquid SO_3 . During this process, trioxane sublimates and precipitates thereby obstructing the equipment.

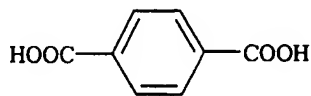
Though a number of other methods failed, it has now been found that 5-carboxyphthalide may be prepared from terephthalic acid in high yields by a convenient, cost-effective procedure.

Description of the invention

Accordingly, the present invention provides a process for the manufacture of 5-carboxyphthalide



comprising reaction of terephthalic acid



with paraformaldehyde, $\text{HO}(\text{CH}_2)_n\text{H}$, in oleum.

By the process of the invention, 5-carboxyphthalide is obtained with very high purity and in high yields (> about 75%). Furthermore, as compared with the prior art process (J. Org. Chem. 1970, 35, p. 1695-1696), the process of the invention takes place without precipitation of sublimated trioxane which obstructs the equipment e.g. by precipitating in condensers.

The oleum used is commercially available oleum. So the following are available from Aldrich/Fluka:

12-17% SO_3 (Fuming sulfuric acid) = 15% oleum

18-24% SO_3 (Fuming sulfuric acid) = 20% oleum

27-33% SO_3 (Fuming sulfuric acid) = 30% oleum

From other sources 20% oleum contains 20-25% SO_3

In the method of the invention, the terephthalic acid is condensed with paraformaldehyde liberating water, which reacts with the SO_3 . When the reaction is complete, 5-carboxyphthalide may be isolated as follows: The reaction mixture is hydrolysed with water. The condensed product, 5-carboxyphthalide inclusive possible diphtalide impurities may then be filtered off, and the 5-carboxyphthalide may be dissolved in aqueous medium by adjusting pH to about 6.7 to 7.3, leaving possible diphtalide impurities in the solid phase. The diphtalide present may be filtered off whereupon 5-carboxyphthalide may be precipitated by acidification, filtered off, washed with water and dried.

Preferably 1.0-1.33 equivalents CH_2O and 1.0-2.5, preferably 1.0-2.0 are used. More preferably 1.25-1.5 equivalents SO_3 per equivalent terephthalic acid are used. Most preferably, about 1.37 equivalents (corresponding to about 3.3 kg 20-25% oleum/kg terephthalic acid) are used per equivalent terephthalic acid.

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The reaction of terephthalic acid with paraformaldehyde is carried out at elevated temperature, conveniently at about 50-148 °C, preferably 115-125°C or 138-148°C. The reaction time is not critical and may easily be determined by a person skilled in the art, a reaction time of 17-21 hours is preferably used for a 210 kg batch at 115-125°C. The time is decreased with increasing temperature.

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The adjustment of pH to 6.3 to 7.3 in order to dissolve the 5-carboxyphthalide formed may be effected by NaOH, e.g. about 10% aqueous NaOH.

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Acidification in order to precipitate the 5-carboxyphthalide may be carried out by adding sulphuric acid until pH = 2.

The terephthalic acid used as a starting material is commercially available.

20 Examples

The invention is further illustrated by the following example.

Example 1

5-Carboxyphthalid

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Terephthalic acid (10 kg) is charged into a reactor. Oleum (20% (18-24% SO_3); 6 kg/kg terephthalic acid) is added and then paraformaldehyde (1.33 equivalents, 0.24 kg/kg terephthalic acid) is added. The mixture is agitated at 125 °C for 17 hours. Water (13 kg/kg terephthalic acid and filter aid is added, the temperature is adjusted to about 70 °C. The precipitate is filtered of, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with NaOH, activated carbon, 0.07 kg/kg terephthalic acid is added, and then the mixture is filtered, the precipitate is rinsed with water. The temperature of the filtrate is adjusted to about 65°C and the pH is adjusted to about 2 with 50% sulfuric acid. The 5-carboxyphthalide precipitated is separated by filtration washed and dried. Yield 83%.

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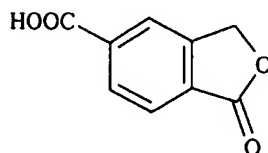
Example 2**5-Carboxyphthalid**

- Oleum (20-25% SO_3 , 43 kg) is charged into a reactor. Terephthalic acid (13 Kg) and then
- 5 paraformaldehyde (3.8 Kg) is added. The mixture is agitated at 138-148 °C for 4½ hours.
- Water (87 L) is added and the temperature is adjusted to about 100 °C. The precipitate is filtered of, washed with water and suspended in water. The pH of the suspension is adjusted to about 7 with NaOH (about 10%), activated carbon, 0.5 Kg is added, and then the mixture is filtered, the precipitate is rinsed with water. The temperature of the filtrate is adjusted to
- 10 about 85°C and the pH is adjusted to about 2 with 96% sulfuric acid. The 5-carboxyphthalide precipitated is separated by filtration washed and dried. Yield 82%.

CLAIMS

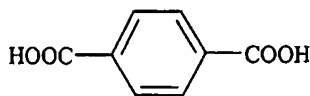
1. A method for the preparation of 5-carboxyphthalide

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comprising reaction of terephthalic acid

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with paraformaldehyde $\text{HO}(\text{CH}_2)_n\text{H}$ in oleum.

2. The method of any of Claim 1 wherein 1.0-1.33 equivalents CH_2O and 1.0-2.5
15 equivalents SO_3 per equivalent terephthalic acid are used
3. The method of Claim 2 wherein 1.0-2.0, in particular 1.25-1.5 equivalents SO_3 per
equivalent terephthalic acid are used.
- 20 4. The method of Claim 3 wherein about 1.37 equivalents SO_3 per equivalent terephthalic
acid are used.
5. The method of Claim 3 wherein about 3.3 kg 20-25% oleum is used per kg terephthalic
acid.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00585

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/88

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3607884 A (LE ROY S. FORNEY), 21 Sept 1971 (21.09.71) --	1-5
X	J. Org. Chem., Volume 36, No 5, 1971, LeRoy S. Forney et al, "The Reaction of Formaldehyde with Deactivated Benzoic Acids. An Ester-Directed Electrophilic Aromatic Substitution Process" page 689 - page 693 --	1-5
X	DE 2242007 A1 (BASF AG), 14 March 1974 (14.03.74), page 2 --	1-5

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Name and mailing address of the ISA:

Swedish Patent Office
Box 5055, S-102 42 STOCKHOLM
Facsimile No. +46 8 666 02 86

Authorized officer

Gerd Strande11/Eö
Telephone No. +46 8 782 25 00

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International application No.

PCT/DK 00/00585

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of organic chemistry, Volume 35, No 5, May 1970, LeRoy S. Forney, "Reaction of Terephthalic Acid with Formaldehyde in Sulfur Trioxide Media" page 1695 - page 1696 --	1-5
A	DE 2630927 A1 (BASF AG), 19 January 1978 (19.01.78) -- -----	1-5

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/DK 00/00585

Patent document cited in search report			Publication date	Patent family member(s)	Publication date
US	3607884	A	21/09/71	NONE	
DE	2242007	A1	14/03/74	JP 49056970 A	03/06/74
DE	2630927	A1	19/01/78	FR 2357662 A,B GB 1578989 A	03/02/78 12/11/80